REMARKS

Claims 1 and 8-52 are pending in the application. Claims 13-52 are withdrawn from consideration at present. Claims 1, 8, 9 and 12 are amended. In making the amendments, no new matter has been introduced. The claims as amended are supported generally by the specification and claims as filed. Support for the amendments to claim 1 may be found, for example, at page 7, line 12, under the definition for "fibronectin type III domain". Claim 10 is cancelled. Applicants reserve the right to re-introduce any of the amended or cancelled claims in this or future applications. Claims 1 and 8-12 are rejected, and Applicants respectfully traverse the rejections for the reasons set forth as follows:

Rejection under 35 U.S.C. § 101

The Examiner argues that claims 1 and 8-12 are not patentable for lack of utility. The Examiner argues: "While the compound isolated from the library obviously has the asserted utility, the library, per se, does not have a utility, except, to screen a specific compound that has the specific utility. This is analogous to saying that nature (a collection of compounds), which has been the source for isolating specific compounds, is patentable because compounds isolated therefrom have been found to have a specific utility. To date, this has not been the case."

Applicants respectfully contend that the library as claimed satisfies the utility requirement under 35 U.S.C. § 101. Pursuant to MPEP 706.03(a)(1) and the recently published "Utility Examination Guideline" (66 FR 1092, Jan. 5, 2001), the Examiner is required to "review the claims and the supporting written description to determine if the applicant has asserted for the claimed invention any specific and substantial utility that is credible: (a) If the applicant has asserted that the claimed invention is useful for any particular practical purpose (i.e., it has a 'specific and substantial utility') and the assertion would be considered credible by a person of ordinary skill in the art, do not impose a rejection based on lack of utility. . . . An applicant need only provide one credible assertion of specific and substantial utility for each claimed invention to satisfy the utility requirement."

For reasons previously made of record in the Response filed September 12, 2003, and reiterated briefly here, the specification provides specific, substantial and credible utility for the

claimed subject matter. To reiterate: (1) the specification states that a library as claimed can be used for the specific purpose of screening for and identifying a fibronectin domain-based polypeptide that binds to a target molecule of choice (see, e.g., page 3, lines 11-24); (2) the ability to identify proteins that bind to selected target molecules is a substantial utility, as demonstrated by the widespread demand for antibodies that bind to selected antigens (see, e.g., the entire Background of the Invention); and (3) the specification describes the actual use of a subject library to identify a fibronectin domain-based protein that binds and antagonizes a valuable therapeutic target, TNF-alpha (Experimental Results beginning on p.27 of the specification), thus demonstrating that the subject libraries are in fact (not merely "credibly") useful for the aforementioned purposes.

The Examiner, by her own statements, agrees that the library is useful for identifying specific useful compounds contained in the library. However, the Examiner suggests that this utility is no greater than that found in the general "library" of nature.

In response, Applicants respectfully suggest that the subject libraries are, in fact, novel collections of proteins that are particularly suitable for at least one purpose, such as the identification of proteins that bind to a selected target. One could not reasonably screen all of nature to identify, for example, TNF-alpha binding agents. Nor could one reasonably screen almost any other library of proteins (excepting, perhaps, antibody libraries) and expect to identify such binding agents. The subject libraries are selected and described so as to contain a plurality of proteins having a fibronectin type III domain (10Fn3) in which at least three solvent accessible loops are randomized, and it is precisely because of these distinct and novel features that libraries of this nature are useful for identifying binding agents. The mere fact that a library as a whole will not be useful for treating, e.g., inflammation, does not mean the library is useless. Likewise, the mere fact that the library contains component parts that are individually useful for therapeutic purposes should not negative the usefulness of the library as a whole for finding such useful components. Applicants remind the Examiner that screening assays or other methods for identifying compounds that themselves have therapeutic activity are widely patentable. Likewise, instruments for use in pharmaceutical or other biological research, such as microscopes and spectrophotometers, have no use for treating diseases but are nonetheless useful (and therefore patentable) for identifying agents that do treat diseases or accomplish other goals.

A library that is demonstrably useful for identifying useful compounds must therefore also be patentable subject matter.

The Examiner has cited *Brenner v. Manson*. Applicants respectfully remind the Examiner that in *Brenner*, the claimed subject matter was a method for generating a compound with no known use. 383 U.S. 519 at 532 (1966). The presently claimed libraries are compositions of matter that, for example, allow one of ordinary skill in the art to generate compounds with real uses, such as compounds that bind and inhibit TNF-alpha. Accordingly, Applicants disagree with the Examiner's application of *Brenner* to the present case.

Finally, Applicants respectfully draw the Examiner's attention to the fact that numerous issued U.S. patents that claim libraries of peptides or other useful compounds exist, for example, U.S. Pat. Nos., 61,80,343; 6,548,632; 6,696,248. And many companies have been built based on their novel or proprietary libraries of useful compounds including peptides and mimetics (including antibodies), nucleic acids, small molecules, etc. See, e.g., Mimotopes, Domantis, Micromet, Xoma, Clontech (BD Biosciences), etc. Clearly, a library of useful compounds can lead to not only discoveries that confer clinical benefits but also successful business platforms.

Accordingly, Applicants request that the Examiner withdraw the rejection of the pending claims for lack of utility.

Rejection under 35 U.S.C. 112, First Paragraph

"Basic" and "Acidic" Amino Acids

The Examiner maintains a written description rejection of claims 1 and 8-12. It appears that the Examiner is arguing that there is a lack of written description for the criteria by which an amino acid is defined as basic, neutral, or acidic.

Applicants contend that this rejection is untenable for reasons previously made of record. However, for the sole purpose of expediting prosecution, claim 10 is canceled. Claim 10 is the only claim that refers to the disputed categories of amino acids: "basic", "neutral" and "acidic". Accordingly, Applicants believe that the rejection is obviated by cancellation of claim 10, and Applicants reserve the right to re-introduce such claim in this or later patent applications.

"Whole Protein"

The Examiner also sets forth a new ground of rejection by reasoning that the "claim as amended claims any type of library of proteins including a whole protein. [sic] Rather, than only a domain or fragment thereof (i.e., the scaffold portion as in the as-filed specification)" and "is not supported in the as-filed specification."

Applicants do not understand the meaning Examiner seeks to confer upon the claims by suggesting that, in their present form, the claims would encompass "whole proteins". Any polypeptide that, as created, is complete from N-terminus to C-terminus is presumably whole. Nonetheless, for the sole purpose of clarifying the claims so as to make apparent the originally intended meaning, the claims are amended to recite a library of proteins comprising a plurality of fibronectin-based scaffolds which have a variety of structural and functional features. Pages 12 through 17 describe a variety of fibronectin-based scaffolds, and the term "fibronectin type III domain" is defined at page 7, line 12.

Applicants request withdrawal of the rejections of the pending claims for lack of written description.

Rejection under 35 U.S.C. 112, Second Paragraph

The Examiner states that "it is not clear as to the proteins ***derived*** from fibronectin type III domain since, the claim recites it is only a domain, not the whole protein itself."

As noted above, the claims are amended to clarify the intended meaning of the original claims. The term "derived" is eliminated from the claims and replaced with clearly defined structural and chemical characteristics of protein constituents of the subject libraries. Accordingly, Applicants request a withdrawal of the rejection.

With respect the rejection pertaining to Serine, Applicants note that claim 11 clearly recites a sequence of Ser-Gly-Glu, irrespective of how one might choose to characterize Serine. There can be no question that the sequence Ser-Gly-Glu will be understood by one of ordinary skill in the art. Accordingly, Applicants request a withdrawal of the rejection.

Rejection under 35 U.S.C. 102(a)

Claims 1, and 8-12 are rejected as allegedly anticipated by Koide, U.S. Pat. No., 6,462,189 ("Koide").

"A claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described, in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). MPEP 2131.

The Examiner states that Koide "recites at least three randomization of the loops." Applicants respectfully request the Examiner to clarify this statement and reconsider Koide. Although Koide teaches more than one variegation within one loop, it never teaches three randomized loops. Examples IV and V of Koide describes loop variegation in only one of the five loops.

The only example in Koide where more than one loop were variegated or randomized is Example VI, where Koide teaches variegations introduced to both FG and BC loops. Further, in Example XVII, Koide discusses stability measurements of the monobodies, among which monobodies with variegations in both the BC and FG loops (e.g., Ubi4-K) have a significantly lower stability. Based on these stability measurements, Koide teaches that "mutations in the FG loop may have less impact on stability. In addition, the N-terminal tail [which does not belong to any of the five loops, see Figure 1 of Koide] is adjacent to the molecular surface formed by the BC and FG loops (FIGS 1 and 17) and does not form a well-defined structure . . . [and therefore] may be good sites for introducing additional mutations." Column 35, lines 17-25. Thus, Koide does not teach any Fn-based monobdies with at least three randomized loops. At most, Koide teaches a monobody with two variegated loops (BC and FG) and maybe additional mutations in the N-terminal tail, not in any of the other three loops. Koide also teaches away from randomizing another loop in addition to the BC and FG loops, because the other loops have better defined structure than the N-terminal tail and would be expected by Koide as contributing to the stability of the monobodies.

Therefore, Koide does not expressly or inherently teach the element of "at least three randomized loops" and does not anticipate the instant claimed invention.

Further, Koide teaches away from making Fn-based monobdies having more than two randomized loops and does not provide a reasonable expectation of success to modify its

monobodies (e.g., to variegate a third loop in addition to the BC and FG loops) to achieve the present invention.

Accordingly, Applicants respectfully request withdrawal of the rejection of the pending claims for lack of novelty.

CONCLUSION

The Examiner may address any questions raised by this submission to the undersigned at 617-951-7000. Should an extension of time be required, Applicants hereby petition for same and request that the extension fee and any other fee required for timely consideration of this submission be charged to **Deposit Account No. 18-1945.**

Respectfully Submitted,

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